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EXAMINER	
SZPERKA, MICHAEL EDWARD	
ART UNIT	PAPER NUMBER
1644	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PATDOCTC@fr.com

Office Action Summary	Application No.	Applicant(s)	
	10/574,194	URANO, FUMIHIKO	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24-27,32-34,47 and 49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24-27,32-34,47 and 49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response and amendments received July 2, 2009 are acknowledged.

Claims 1-23, 28-31, 35-46, and 48 have been canceled.

Claims 24, 32, 33, and 47 have been amended.

Claim 49 has been added.

Claims 24-27, 32-34, 47, and 49 are pending in the instant application.

Note that the dependency of claim 47 has been changes such that it now depends from independent claim 24, and as such is now part of the elected invention of Group III as they read on screening assays.

Claims 24-27, 32,-34, 47, and 49 are under examination in this office action.

Specification

2. Applicant's amendments to the title and abstract acknowledged.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. The rejection of claim 33 under 35 U.S.C. 112, second paragraph, as being indefinite because of circular dependency by applicant's claim amendments received July 2, 2009 which correct the dependency issue.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. The rejection of claims 24-27, 33, and 34 under 35 U.S.C. 102(b) as being anticipated by Bertolotti et al. (Nature Cell Biology, 2000, 2:326-332) has been withdrawn in view of applicant's claim amendments received July 2, 2009.

Specifically, the independent claim has been amended to recite the use of an antibody which is specific for the phosphorylated form of IRE1 and the antibody used by Bertolotti et al. binds to all forms of IRE1 (phosphorylated and non-phosphorylated).

7. Claims 24-27, 33 and 34 stand rejected, claim 32 as presently amended is rejected, and newly presented claim 49 is rejected under 35 U.S.C. 102(e) as being anticipated by Ron et al. (US 2003/0224428 A1, of record) for the reasons of record. The office action mailed January 2, 2009 states:

> Ron et al. disclose screening methods to identify agents that alter the phosphorylation of IRE1 using antibodies that bind to the phosphorylated form of IRE1 (see entire document, particularly the abstract, paragraphs 22-26, 38, and claims 1-3 and 14-17). Ron et al. also disclose that agents such as tunicamycin, thapsigargin, and DTT are used to increase ER stress in their model systems (paragraphs 15, 60, 64, 67-83).
>
> Therefore, the prior art anticipates the claimed invention.

Applicant's arguments filed July 2, 2009 have been fully considered but they are not persuasive. Applicant argues that Ron et al. is not a proper anticipatory reference because it does not teach a specific method for making antibodies that bind the phosphorylated form of IRE1 and that no working example using such antibodies is disclosed. Since applicant argues that such antibodies are hard to make, the disclosure of Ron et al. is not enabled.

This argument is not persuasive. Applicant is reminded that while working examples are useful and desirable, they are not required to demonstrate enablement as

per MPEP 2164.02. Ron et al. clearly conceived detection of phosphorylated IRE1 by use of phosphorylation specific antibodies as is demonstrated not only by paragraph 38 as was quoted by applicant but also by dependent claims 14-17. Applicant is also reminded that the specification is not required to teach a skilled artisan what he already knows (if it were, specifications would be incomprehensibly large). Antibodies that specifically discriminate between phosphorylated and non-phosphorylated forms of the same antigen were well known in the art at the time of the instant invention, such antibodies being generated by immunization with full length phosphorylated proteins and with shorter phosphopeptides as evidenced by Sternberger et al., Blaydes et al., Mandell, and US Patent 5,599,681. Note that as of 2003, the year in which the earliest priority documents to which the instant application claims priority were filed, over 300 phosphorylation state specific antibodies were commercially available as demonstrated by Table 1 of Mandell. Thus it appears that the generation of phosphospecific antibodies is routine in the art, and indeed line 11 of page 39 of the instant specification states "The antibodies were produced using standard methodology" when describing how antibody PIRE1A1 was generated. Thus, given the high number of prior art antibodies, the detailed protocols disclosed in the prior art, and the disclosure of the instant specification that only standard methods were used indicates that while making such phosphorylation specific proteins might be laborious and of low yield the effort required to make such an antibody is not unpredictable in the same way that it was held that screening for a desired monoclonal antibody was not unpredictable in In re Wands. Thus Ron et al. do not need to teach artisans how to make such antibodies because suck knowledge is present and well known in the prior art.

Applicant has further argued that the specific phosphorylation site within IRE1 was not known and that thus there is no direction or motivation to immunize with a peptide “having” the amino acid sequence of SEQ ID NO:20. To support this argument applicant has supplied the Shamu et al. and Papa et al. references.

This argument is not persuasive. First, Ron et al. state that “Because the phosphorylation site***s*** on IRE1 are known, anyone skilled in the art can develop an antiserum or monoclonal antibody..." (emphasis added by the examiner) and the instant

specification discloses on page 39 that "The phosphorylation site of Ire1α is conserved from lower eukaryotes to humans (Shamu and Walter, Embo J 15:3028-39 (1996); Tirasophon et al., Genes Dev 12:1812-24 (1998))." Thus, both disclosures indicate that the requisite epitope is known in the prior art. Applicant has argued that based on Shamu et al., there are three possible resides that could be phosphorylated. Apart from claim 49, the instant claims require no particular form of phosphorylated IRE1 to be detected, and as evidenced by Shamu et al., IRE1 is phosphorylated at multiple positions. Thus, an antibody specific for any or all of the disclosed positions would meet the instant claim limitations. Turning to claim 49, the prior art does not indicate that the three residues are equally important. Indeed, the mutation data of Shamu et al. indicate that the single mutation which yielded the greatest impact upon phosphorylation occurred at position 841 (see entire document, particularly the right column of page 3035). Further, the alignment of yeast IRE1 with mouse and *C. elegans* IRE1 sequences as was done in Figure 1A of Wang et al. and the alignment of yeast IRE1 with human and *C. elegans* IRE1 sequences as was done in Figure 1C of Tirasophon et al. indicate that the serine corresponding to position 841 of the yeast sequence is the only serine which is conserved among all the sequences. Note that the Tirasophon et al. reference which discloses the conservation of the serine residue is the same reference cited by applicant in the instant specification and thus artisans at the time the invention was made were well aware of which residues were and were not conserved within IRE1. Therefore, in contrast to applicant's argument that a skilled artisan would have three residues to choose from, it is clear that an artisan would choose the residue which is conserved among all sequences. Indeed, the instant specification does not disclose that any inquiry was set forth to determine the phosphorylation site or that it was unexpected that the sixth residue of the peptide of SEQ ID NO:20 was phosphorylated.

Additionally, claim 49 recites immunizing with a peptide "having" SEQ ID NO:20. The term "having" is considered to be open sequence language equivalent in meaning to "comprising" such that additional sequence can be added to either or both ends of the sequence. As such, it reads upon immunization with a full length phosphoprotein,

just as was done in the production methods disclosed by Sternberger et al. Since the native phosphoprotein is phosphorylated at the recited location, antibodies produced using the methods of Sternberger et al. would comprise the recited specificity. Note that as presently written, the antibody used in the method of claim 49 is recited as a product by process limitation. As per MPEP 2113, "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985). Given that the process recited in claim 49 does not appear to make an antibody product that is different from that disclosed in the prior art for the reasons discussed above, claim 49 has been joined to the rejection of record. Also, claim 32 has been amended to recite decreasing IRE1 activity rather than increasing activity as had been previously presented, and thus claim 32 has also been joined to the rejection of record.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. The rejection of claim 32 under 35 U.S.C. 103(a) as being unpatentable over Ron et al. (US 2003/0224428 A1, of record) in view of Kaufman et al. (US 2005/0250182 A1) has been withdrawn in view of applicants claim amendments which remove the limitation of increasing IRE1 activity and replace it with decreasing IRE1 activity.

10. The following are new grounds of rejection necessitated by applicant's claim amendments received July 2, 2009.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claim 33 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, claim 32 recites "candidate therapeutic compound" while its dependent claim 33 recites "candidate therapeutic agent". Are the "compound" and "agent" the same thing, or are they different molecules? Clarification of the metes and bounds of the terms used in the instant claims will likely be beneficial in obviating this rejection.

13. Claim 47 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ron et al. (US 2003/0224428 A1, of record) as applied to claims 24-27, 32-34, and 49 above, and further in view of Harding et al. (Diabetes, 2002, 51:supplement 3, s455-s461).

The teachings of Ron et al. have been discussed above and differ from the instant claimed invention in that while Ron et al. disclose multiple ER stress models for use in their disclosed screening methods, they do not disclose models of diabetes or that diabetes is an ER stress disorder.

Harding disclose that ER stress is caused when there is an imbalance between the amount of proteins made and the amount which can be properly folded such that improperly folded polypeptides accumulate in the ER, and that while ER stress can occur in any cell type, the problem is most acute in professional secretory cells (see entire document, particularly the abstract and page s455). It is further disclosed that β-cells secrete large amounts of insulin, that the development of diabetes is linked to ER

stress, and that the Akita mouse can be used to probe the connections between ER stress, β-cell function, and the progression of diabetes (see particularly page s458).

Therefore, it would have been obvious to a person of ordinary skill in the art at the time the instant invention was made to use a diabetic model when performing the methods of Ron et al. This is because as per the teachings of Harding et al. ER stress is increased in diabetes and Ron et al. disclose methods of monitoring and screening for inhibitors of ER stress by using antibodies that bind the ER stress marker phosphorylated IRE1.

Claim Objections

14. Claim 32 is objected to in that the word "test" is misspelled in line 6 of the claim.

15. No claims are allowable.

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is (571)272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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